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The impact of kidney function on outcomes following high risk myocardial infarction: findings from 27 610 patients

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Aims Renal dysfunction is associated with poor cardiovascular outcome. We investigated the relationship of kidney function and long-term cardiovascular outcomes in patients with high risk myocardial infarction.

Methods and results We studied 27 610 patients from four randomized trials of acute myocardial infarction complicated by heart failure and/or LV dysfunction (LVEF ≤40%). Two trials excluded patients with serum creatinine ≥2.5 mg/dL. Patients were grouped by estimated glomerular filtration rate (eGFR) using the four-component Modification of Diet in Renal Disease equation. We used adjusted Cox proportional hazard models to compare mortality and composite cardiovascular events among eGFR groups. Median follow-up was 23 months. The eGFR was approximately normally distributed, with a mean ± SD of 69.1 ± 20.2 mL/min/1.73 m^2. Co-morbidities were more prevalent with lower eGFR. The risk of death or composite outcome of cardiovascular death, myocardial infarction, stroke, or heart failure hospitalization increased with declining eGFR. Below 75 mL/min/1.73 m^2, each 10 unit reduction of eGFR was associated with an adjusted hazard ratio for death of 1.13 (95% confidence interval, 1.11–1.15) and composite cardiovascular outcome of 1.09 (95% confidence interval, 1.08–1.10). Older patients (≥75 years) with low LVEF (<30%) had a higher incidence of mortality and adverse cardiovascular events across eGFR categories.

Conclusions Reduced eGFR is strongly and independently associated with poor cardiovascular outcome following high risk myocardial infarction. In these patients, the combination of older age and poor LV systolic function is associated with increased risk of adverse events.

Keywords Kidney function • Glomerular filtration rate • Myocardial infarction • Cardiovascular outcomes

Introduction

The burden of kidney disease is increasing across various populations, mainly because of ageing and the prevalence of co-morbidities such as diabetes and hypertension.[1–3] Chronic kidney dysfunction is a risk factor for poor cardiovascular outcome.[4] Population-based studies have found an increased risk of incident myocardial infarction, cardiovascular mortality, and all-cause mortality in subjects with chronic kidney dysfunction manifested by a reduced glomerular filtration rate (GFR).[5–7]

Reduced renal function appears to confer an increased risk of mortality and adverse cardiovascular events after myocardial infarction.[8] Patients with end-stage renal disease have twice the 2-year mortality after myocardial infarction of patients with normal renal function.[4] In large registries of all-comers with acute myocardial infarction, worsening creatinine during hospitalization had a graded association with long-term mortality.[9,10] The importance

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of kidney function in patients with high risk (complicated by ventricular dysfunction, and/or heart failure) myocardial infarction was highlighted in a post-hoc analysis of the VALIANT trial[11] where reduced GFR was associated with increased risk of death and non-fatal cardiovascular events.

Although the majority of these studies yielded consistent results, most of them are retrospective in nature, and most included a heterogeneous population of patients. In addition, they included few subjects with a low GFR and therefore failed to answer several important related questions, such as the significance of kidney function in the lower end of the spectrum (GFR <45 mL/min/1.73 m^2), the differential risk of ischaemic cardiac events vs. heart failure development with worse kidney function, and the interplay of factors such as age and LV function in the modulation of the risk conferred by renal dysfunction.

The High-Risk Myocardial Infarction Database Initiative[12] combined the databases of four large randomized trials that enrolled patients with high risk myocardial infarction with similar characteristics, and provides the opportunity to explore answers to the above questions in a large prospective group of patients. We analysed participants enrolled in the VALIANT,[13] EPHESUS,[14] OPTIMAAL,[15] and CAPRICORN[16] trials as a stratified cohort of patients with high risk myocardial infarction. This report focuses on the importance of kidney function as a correlate for and a predictor of long-term cardiovascular outcomes. We explore these relationships at both ends of the GFR spectrum and examine how they may be affected by the interaction of age and LV systolic function in this patient population.

Methods

Patients

Patients were enrolled in one of the four trials if up to 3 weeks prior to randomization they had acute myocardial infarction complicated by clinical and/or radiographic signs of heart failure, LV dysfunction (LVEF ≤40%), or both. Details of inclusion and exclusion criteria for each trial have been published previously.[17–20] The VALIANT and EPHESUS trials excluded patients with significant renal impairment (serum creatinine ≥2.5 mg/dL). The LVEF was measured by echocardiography, or contrast or radionuclide ventriculography. Mean follow-up duration ranged from 16 to 32 months in the four trials. The current analysis only includes patients who had documented creatinine measurement at baseline.

Definition of kidney disease

The National Kidney Foundation 2002 Practice Guidelines define chronic kidney disease as the presence of kidney damage or a GFR of <60.0 mL/min/1.73 m^2 of body surface area for ≥3 months.[10] Kidney damage is evidenced by the presence of pathological abnormalities or abnormal laboratory or imaging studies. Thus some patients can have kidney damage even in the presence of a normal or mild reduction in GFR.[10] A GFR of <60 mL/min/1.73 m^2 is considered the cut-off value for chronic kidney disease since it indicates a significant reduction (by more than half) compared with normal function.[4] In accordance with these guidelines, we classified patients enrolled in the high risk myocardial infarction trials according to their estimated GFR (eGFR).

Estimation of the glomerular filtration rate

The GFR is considered the most suitable variable for quantifying renal function.[21] To estimate the GFR (eGFR), we used the four-component Modification of Diet in Renal Disease (MDRD) equation,[4] which incorporates age, race, sex, and serum creatinine level:[4,22]

$$\text{eGFR (mL/min/1.73 m}^2) = 186 \times [\text{serum creatinine level (mg/dL)}]^{-1.154} \times (\text{age [years]})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}).[4]$$

Characteristics and outcomes recorded

Baseline demographics, risk factors, and clinical characteristics at the time of the myocardial infarction were recorded for each trial. An expert Endpoint committee adjudicated all events in each of the trials. The trials had similar definitions of various endpoints.[12] The primary outcome in our analysis was death from any cause. Secondary outcomes were death from cardiovascular causes, heart failure hospitalization, recurrent myocardial infarction, and stroke. Together, these formed the cardiovascular composite outcome for our analysis.

Statistical analysis

Patients were categorized according to their eGFR at baseline. A total of 27 610 patients had baseline creatinine values recorded. The analysis excluded those subjects who had missing baseline eGFR data or baseline eGFR >140 (93 patients, probably due to erroneous data entry). The distribution of eGFR was divided into six categories (<30.0, 30.0–44.9, 45–59.9, 60–74.9, 75.0–124.9, and 125.0–139.9 mL/min/1.73 m^2).

Common baseline characteristics across the four studies are presented by eGFR category. Values are reported as percentages for categorical variables and as means with standard deviations (SDs) for continuous variables. Cox proportional hazards models adjusted by study were used to estimate the hazard of clinical outcomes and to adjust for baseline covariates. Selected potential interactions were also explored. Kaplan–Meier estimates, stratified according to the eGFR, for death from any cause and the cardiovascular composite outcome were determined and presented as event curves. To explore potential interactions with age and LVEF, we examined outcomes across eGFR categories using the cut-offs of 75 years for age and 30% for LVEF. All *P*-values were two-sided, with *P*-values <0.05 considered statistically significant. Analyses were performed using SAS software (version 9.2).

Results

Baseline characteristics

The baseline eGFR for the 27 610 patients was approximately normally distributed (see Supplementary material, *Figure S1*) with mean ± SD of 69.1 ± 20.2 mL/min/1.73 m^2 (10th and 90th percentiles of 44.1 and 95.2, respectively). *Table 1* shows the

Table 1 Demographics and baseline characteristics across renal function categories

Baseline characteristic	Baseline eGFR categories (mL/min/1.73 m^2)						
	<30, *n* = 388	30–45, *n* = 2616	45–60, *n* = 6264	60–75, *n* = 8435	75–125, *n* = 9616	125–140, *n* = 291	Total, *n* = 27 610
Age (years)							
Mean ± SD	74.8 ± 8.3	73.4 ± 8.9	69.9 ± 9.5	65.1 ± 10.5	59.6 ± 11.0	55.4 ± 11.3	65.1 ± 11.4
Percentiles (25, med, 75)	70, 76, 80	68, 74, 79	64, 71, 77	58, 66, 73	52, 59, 68	47, 53, 63	57, 66, 74
Sex, *n* (%)							
Male	113 (29)	1286 (49)	3682 (59)	6151 (73)	7916 (82)	220 (76)	19 368 (70)
Female	275 (71)	1330 (51)	2582 (41)	2284 (27)	1700 (18)	71 (24)	8242 (30)
Race, *n* (%)							
Caucasian	373 (96)	2487 (95)	5934 (95)	7963 (94)	8881 (92)	251 (86)	25 889 (94)
Black	1 (<1)	31 (1)	74 (1)	115 (1)	248 (3)	21 (7)	490 (2)
Asian	2 (1)	24 (1)	61 (1)	84 (1)	111 (1)	0	282 (1)
Other	12 (3)	74 (3)	195 (3)	273 (3)	376 (4)	19 (7)	949 (3)
Systolic BP (mmHg)							
Mean ± SD	126.6 ± 20.4	125.1 ± 18.6	123.7 ± 17.7	121.4 ± 16.4	119.5 ± 15.9	118.9 ± 16.5	121.7 ± 16.9
Percentiles (25, med, 75)	110, 120, 140	110, 120, 136	110, 120, 133	110, 120, 130	110, 119, 130	108, 116, 130	110, 120, 130
Diastolic BP (mmHg)							
Mean ± SD	70.9 ± 12.9	71.7 ± 11.8	72.4 ± 11.5	72.1 ± 10.8	71.9 ± 10.7	72.7 ± 11.5	72.1 ± 11.1
Percentiles (25, med, 75)	60, 70, 80	62, 70, 80	64, 70, 80	65, 70, 80	65, 70, 80	65, 70, 80	64, 70, 80
Heart rate (b.p.m.)							
Mean ± SD	75.0 ± 12.1	76.2 ± 13.4	75.8 ± 13.0	75.1 ± 12.8	76.0 ± 12.6	77.2 ± 13.0	75.7 ± 12.8
Percentiles (25, med, 75)	66, 75, 82	67, 75, 84	68, 75, 84	66, 74, 82	68, 75, 84	68, 76, 85	67, 75, 83
Body mass index (kg/m^2)							
Mean ± SD	27.4 ± 5.4	27.5 ± 4.8	27.5 ± 4.7	27.5 ± 5.0	27.6 ± 4.8	27.4 ± 5.1	27.5 ± 4.8
Percentiles (25, med, 75)	24, 27, 30	24, 27, 30	24, 27, 30	24, 27, 30	24, 27, 30	24, 27, 30	24, 27, 30
KILLIP class, *n* (%)							
1	58 (15)	493 (19)	1385 (22)	2363 (28)	3089 (32)	87 (30)	7475 (27)
2	173 (45)	1336 (51)	3372 (54)	4582 (55)	5053 (53)	148 (51)	14 664(53)
3	120 (31)	590 (23)	1163 (19)	1142 (14)	1090 (11)	42 (14)	4147 (15)
4	35 (9)	188 (7)	317 (5)	314 (4)	346 (4)	13 (4)	1213 (4)
LVEF (%)							
Mean ± SD	33.5 ± 9.3	33.4 ± 9.2	34.0 ± 9.0	34.5 ± 8.8	34.8 ± 9.0	34.9 ± 9.1	34.4 ± 9.0
Percentiles (25, med, 75)	29, 33, 38	28, 33, 38	30, 34, 38	30, 35, 39	30, 35, 38	30, 35, 39	30, 35, 38

Column header counts are the number of subjects in each eGFR category. A total of 176 VALIANT subjects, 143 OPTIMAAL subjects, 728 CAPRICORN subjects, and 114 EPHESUS subjects who had missing baseline eGFR data or eGFR ≥140 are not included in the table. Percentages (%) are calculated using subjects with non-missing data.
BP, blood pressure; eGFR, estimated glomerular filtration rate; med, median; SD, standard deviation.

distribution of the eGFR. Of these patients, 9268 (33.6%) met the criteria for kidney disease (cut-off of eGFR <60).

The mean (± SD) age of the patients was 65.1 ± 11.4 years, and 70% were males. Patients with lower eGFR values were more likely to be older and female than patients with higher eGFR. The vast majority of the patients enrolled in the four trials were Caucasians, with blacks constituting less than ~2% of the overall sample. Patients with lower eGFR had a higher systolic blood pressure at baseline, weighed less, and were less likely to have a current or past history of smoking than those with higher eGFR. The LVEF was not collected in OPTIMAAL. Mean LVEF was 34.4 ± 9.0% in the other three studies and was similar across the eGFR categories; however, patients with lower eGFR had on average a more advanced Killip class at the time of myocardial infarction in the overall population. The prevalence of co-morbidities such as diabetes, hypertension, history of angina, prior myocardial infarction, heart failure, and COPD increased gradually with decreasing eGFR. Cerebrovascular and peripheral vascular diseases were more common in patients with renal dysfunction (*Table 2*).

Outcomes

During a median follow-up of 717 days (23 months), 4945 patients (18%) died and 8180 (30%) experienced the composite cardiovascular outcome.

When eGFR was modelled as a continuous variable with the hazard ratio calculated across a range of eGFR values using a reference value of 75.0 mL/min/1.73 m^2, the relationship between the hazard ratio and the eGFR was curvilinear, with a steeper increase in hazard at lower eGFR values (*Figure 1*). In the adjusted model, each 10 unit decrease in the value was associated with a hazard ratio of 1.13 [95% confidence interval (CI) 1.11–1.15,

Table 2 Medical history and baseline medications across renal function categories

Disease history	Baseline eGFR category (mL/min/1.73 m^2)						
	<30, *n* = 388	30–45, *n* = 2616	45–60, *n* = 6264	60–75, *n* = 8435	75–125, *n* = 9616	125–140, *n* = 291	Total, *n* = 27 610
Diabetes	158 (41)	949 (36)	1785 (28)	1981 (23)	2205 (23)	93 (32)	7171 (26)
Type II	106 (27)	719 (27)	1358 (22)	1547 (18)	1707 18)	69 (24)	5506 (20)
Hypertension	301 (78)	1786 (68)	3784 (60)	4302 (51)	4551 (47)	154 (53)	14878 (54)
Previous MI	161 (41)	931 (36)	1825 (29)	2022 (24)	2150 (22)	59 (20)	7148 (26)
Atrial fibrillation	93 (24)	554 (21)	1057 (17)	1007 (12)	914 (10)	19 (7)	3644 (13)
Dyslipidaemia	197 (51)	1173 (45)	2809 (45)	4130 (49)	4735 (49)	133 (46)	13 177 (48)
Renal insufficiency	129 (33)	404 (15)	279 (4)	83 (1)	22 (<1)	0	917 (3)
Heart failure	221 (57)	1402 (54)	2730 (44)	2969 (35)	3306 (34)	111 (38)	10 739 (39)
COPD	51 (13)	248 (9)	564 (9)	663 (8)	726 (8)	23 (8)	2275 (8)
Cerebrovascular accident	59 (15)	339 (13)	633 (10)	603 (7)	537 (6)	20 (7)	2191 (8)
PVD	59 (15)	326 (12)	623 (10)	625 (7)	611 (6)	21 (7)	2265 (8)
Smoking history							
Never	235 (61)	1328 (51)	2842 (45)	3013 (36)	2505 (26)	68 (23)	9991 (36)
Current	37 (9)	359 (14)	1312(21)	2595 (31)	4310 (45)	157 (54)	8770 (32)
Past	115 (30)	924 (35)	2101 (34)	2816 (33)	2793 (29)	66 (23)	8815 (32)
Baseline medication use	**<30, *n* = 388**	**30–45, *n* = 2614**	**45–60, *n* = 6262**	**60–75, *n* = 8432**	**75–125, *n* = 9614**	**125–140, *n* = 291**	**Total, *n* = 27 601**
ACE inhibitor[a]	189 (56)	1221 (55)	2719 (54)	3468 (54)	4330 (54)	148 (52)	12 075 (54)
ARB[a]	11 (3)	41 (2)	105 (2)	90 (1)	90 (1)	4 (1)	341 (2)
Diuretic	272 (70)	1671 (64)	3371 (54)	3590 (43)	3564 (37)	117 (40)	12 585 (46)
Aldosterone antagonist[b]	1 (4)	4 (3)	11 (4)	5 (1)	1 (<1)	0	22 (2)
Aspirin	327 (84)	2221 (85)	5376 (86)	7336 (87)	8523 (89)	262 (90)	24 045 (87)
Antiplatelet (excluding aspirin)[a]	62 (18)	405 (18)	1074 (22)	1676 (26)	2658 (33)	105 (37)	5980 (27)
Vitamin K antagonist	49 (13)	285 (11)	675 (11)	862 (10)	937 (10)	35 (12)	2843 (10)
Calcium channel blocker	61 (16)	332 (13)	626 (10)	676 (8)	609 (6)	16 (5)	2320 (8)
Beta-blocker[c]	205 (57)	1481 (60)	3753 (63)	5347 (66)	6518 (71)	226 (79)	17 530 (66)
Statin	112 (29)	721 (28)	1979 (32)	3001 (36)	3716 (39)	116 (40)	9645 (35)
Digitalis	75 (19)	430 (16)	868 (14)	807 (10)	877 (9)	30 (10)	3087 (11)

Values are *n* (%).
Column header counts are the number of subjects in each baseline eGFR category. A total of 176 VALIANT subjects, 143 OPTIMAAL subjects, 728 CAPRICORN subjects, and 114 EPHESUS subjects who had missing baseline eGFR data or eGFR ≥140 are not included in the table.
eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PVD, peripheral vascular disease.
[a]Denominators are all CAPRICORN, EPHESUS, and VALIANT subjects who have a baseline medication record and baseline eGFR data (*n* = 22 269).
[b]Denominators are all CAPRICORN subjects who have a baseline medication record and baseline eGFR data (*n* = 1231).
[c]Denominators are all EPHESUS, OPTIMAAL, and VALIANT subjects who have a baseline medication record and baseline eGFR data (*n* = 26 370).

$P < 0.001$] for death and 1.09 (95% CI 1.08–1.10), $P < 0.001$) for the composite cardiovascular outcome.

Lower eGFR was associated with higher mortality as well as higher incidence of the various cardiovascular outcomes (*Table 3*). Unadjusted Kaplan–Meier estimates of 3-year mortality increased with decreasing eGFR (*Table 4*). A similar pattern of increasing event rates with lower eGFR was seen with the composite cardiovascular outcome and its individual components; stratified log-rank $P < 0.001$ for all outcomes (see Supplementary material, *Figure S2*).

There was a wide spectrum of risk across the categories of eGFR, with early divergence of the Kaplan–Meier curves for both death and the composite outcome (*Figure 2*). The risk of events appears to be highest during the first 3 months after myocardial infarction; however, it continued to increase throughout the duration of follow-up.

Using the group with an eGFR of 75.0–124.9 mL/min/1.73 m^2 as the referent group yielded hazard ratios for death from any cause and the composite endpoint that increased as the degree of renal impairment increased (*Table 4*). After adjustment for baseline characteristics in the multivariate model, the relationship of increased hazard of death and of the composite outcome was less pronounced but still highly statistically significant.

Potential interaction with left ventricular ejection fraction and age

For mortality, an interaction between eGFR category and LVEF (categorized using 30% as a cut-off) was statistically significant

Table 3 Endpoints across renal function categories

Outcome	Baseline eGFR categories (mL/min/1.73 m^2)						
	<30, *n* = 388	30–45, *n* = 2616	45–60, *n* = 6264	60–75, *n* = 8435	75–125, *n* = 9616	125–140, *n* = 291	Total, *n* = 27 610
Death	184 (47)	902(34)	1444(23)	1284(15)	1105(11)	26(9)	4945(18)
Cardiovascular (CV) death	162(42)	790(30)	1251(20)	1089(13)	923(10)	23(8)	4238(15)
HF hospitalization	96(25)	596(23)	944(15)	865(10)	743(8)	17(6)	3261(12)
MI (fatal or non-fatal)	83(21)	472(18)	824(13)	852(10)	791(8)	14(5)	3036(11)
Stroke (fatal or non-fatal)	16(4)	143(5)	228(4)	271(3)	241(3)	7(2)	906(3)
Resuscitated sudden death[a]	49(13)	277(11)	536(9)	545(6)	541(6)	14(5)	1962(7)
Composite endpoint							
CV death, non-fatal MI, non-fatal stroke, or HF hospitalization	227(59)	1301(50)	2259(36)	2284(27)	2055(21)	54(19)	8180(30)

Values are *n* (%).
Column header counts are the number of subjects in each baseline eGFR category. A total of 176 VALIANT subjects, 143 OPTIMAAL subjects, 728 CAPRICORN subjects, and 114 EPHESUS subjects who had missing baseline eGFR data or eGFR ≥140 are not included in the table.
eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction.
[a]Resuscitated sudden death for EPHESUS, OPTIMAAL, and VALIANT; sudden death for CAPRICORN.

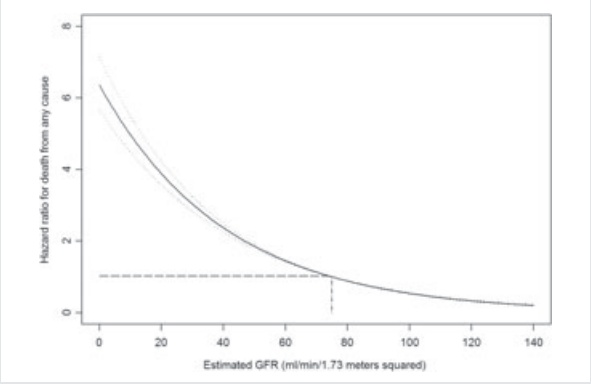

Figure 1 Unadjusted hazard ratio for death from any cause, according to estimated glomerular filtration rate (GFR) at baseline. The dotted lines represent the 95% confidence limits of the estimate.

for the model adjusting for additional baseline covariates, specifically in the eGFR 30–44.9 mL/min/1.73 m^2 group. In those patients with LVEF <30%, the hazard ratio for death in the eGFR 30–44.9 mL/min/1.73 m^2 group compared with patients in the eGFR 75.0–124.9 mL/min/1.73 m^2 group was 2.10 (95% CI 1.80–2.46) and, in the LVEF ≥30% group, the hazard ratio was 1.56 (95% CI 1.32–1.85) (*Table 5*). Both LVEF groups showed a graded relationship between eGFR and outcome. OPTIMAAL did not collect LVEF; therefore, these results exclude OPTIMAAL patients. The overall interaction between eGFR category and LVEF was also significant for the composite outcome in a model adjusting for other baseline covariates. The interaction can be seen in *Figure 3* and in Supplementary material, *Table S1*, which show the percentage of death and the composite endpoint across different eGFR, age, and LVEF categories. Overall, the highest incidence occurred in patients older than 75 years whose LVEF was <30%. The lowest incidence occurred in patients younger than 75 years whose LVEF was >30%.

Discussion

We have demonstrated that reduced eGFR in patients with high risk acute myocardial infarction was associated with poor long-term cardiovascular outcome. This relationship, present across the spectrum of eGFR, showed a graded association, with more severe reduction in eGFR values associated with the worst prognosis. Furthermore, the finding was independent of other risk factors traditionally known to predict or be associated with increased incidence of adverse events.

Our findings are consistent with previous studies. We confirmed the results of the prior VALIANT analysis[11] in a larger cohort of similar patients. The present combined analysis provides much more precise estimates. Also, a large single-centre retrospective study found an increased risk of in-hospital mortality even with mild renal dysfunction.[23] In a small registry study of 754 patients post-myocardial infarction, Schiele *et al.* found a significant association between decreased eGFR and higher mortality at 1 year even after adjustment for baseline risk.[24] We found that the increased risk associated with renal dysfunction manifests early following myocardial infarction and persists over long-term follow-up. There was no difference in the incidence of ischaemic (stroke, myocardial re-infarction) vs. heart failure events; the relative frequencies of these events were similar within the different categories of renal dysfunction (*Table 3*).

More recently, an analysis of patients with established vascular disease enrolled in the BRAVO trial showed that patients with a GFR ≥125 mL/min/1.73 m^2 were at increased risk for major cardiovascular events.[25] This phenomenon might be attributed to an overestimation of the GFR from underlying cachexia and decreased muscle mass causing reduced serum creatinine levels. In contrast to the findings from the BRAVO trial, we did not find

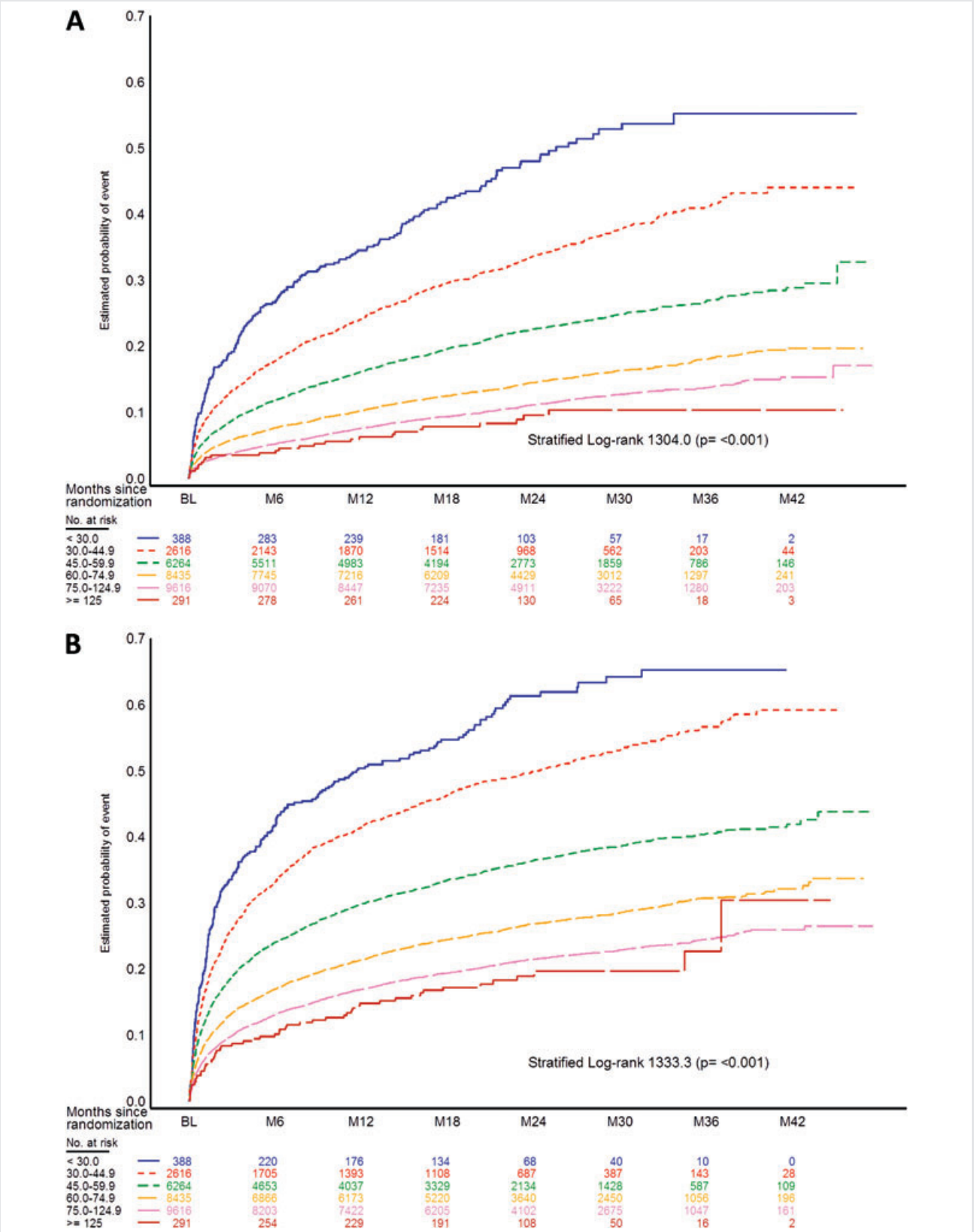

Figure 2 Kaplan–Meier curves for mortality (*A*) and the composite outcome (*B*) by estimated glomerular filtration rate category.

Table 4 Hazard ratio and estimates of 3-year event rates of all-cause death and the composite endpoint associated with different categories of estimated glomerular filtration rate

Endpoint	eGFR category (mL/min/1.73 m^2)	Hazard ratios from a Cox proportional hazard model			Kaplan–Meier estimates of 3-year mortality	
		HR	95% CI	*P*-value	Event rate	95% CI
Death—unadjusted	<30	5.45	4.66–6.37	0.005	55.2	48.7–61.6
	30–44.9	3.52	3.23–3.85		40.9	38.5–43.3
	45–59.9	2.19	2.02–2.37		26.4	25.1–27.7
	60–74.9	1.38	1.27–1.49		17.9	16.9–18.9
	75–124.9	1	—		13.6	12.7–14.4
	125–139.9	0.76	0.52–1.12		10.3	6.4–14.2
Death—adjusted[a]	<30	2.74	2.31–3.21	0.005		
	30–44.9	1.85	1.67–2.03			
	45–59.9	1.42	1.30–1.55			
	60–74.9	1.13	1.04–1.23			
	75–124.9	1	—			
	125–139.9	0.80	0.53–1.18			
Death—adjusted[b]	<30	2.79	0.27–3.42	0.004		
	30–44.9	1.82	1.61–2.06			
	45–59.9	1.48	1.34–1.64			
	60–74.9	1.15	1.04–1.27			
	75–124.9	1	—			
	125–139.9	0.73	0.47–1.14			

Endpoint	eGFR category (mL/min/1.73 m^2)	Cox proportional hazard model			Kaplan–Meier estimates of 3-year mortality	
		HR	95% CI	*P*-value[a]	Event rate	95% CI
Composite—unadjusted	<30	3.79	3.30–4.35	0.002	65.2	59.4–71.0
	30–44.9	2.9	2.70–3.11		56.4	53.9–58.8
	45–59.9	1.9	1.79–2.02		40.2	38.8–41.6
	60–74.9	1.32	1.24–1.40		30.6	29.5–31.8
	75–124.9	1	—		24.3	23.3–25.3
	125–139.9	0.85	0.65–1.12		22.6	15.2–30.1
Composite—adjusted[a]	<30	1.97	1.70–2.28	<0.001		
	30–44.9	1.63	1.50–1.76			
	45–59.9	1.31	1.23–1.40			
	60–74.9	1.12	1.05–1.19			
	75–124.9	1	—			
	125–139.9	0.84	0.64–1.11			
Composite—adjusted[b]	<30	1.96	1.64–2.33	<0.001		
	30–44.9	1.61	1.47–1.77			
	45–59.9	1.34	1.24–1.45			
	60–74.9	1.12	1.04–1.21			
	75–124.9	1	—			
	125–139.9	0.81	0.60–1.10			

Patients with an eGFR of 75–124.9 mL/min/1.73 m^2 constitute the referent group.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
P-value is a 1 df test testing for monotone effect of eGFR category on estimated HR.
[a]Adjusted for: age, gender, race, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, smoking history, Killip class, history of diabetes, hypertension, angina, previous myocardial infarction, AF, dyslipidaemia, heart failure, COPD, cerebrovascular disease, peripheral vascular disease.
[b]Adjusted for the above, plus LV function (this excludes OPTIMAAL patients from the analysis).

that patients with an eGFR between 125 and 140 mL/min/1.73 m^2 post-high risk myocardial infarction were at increased risk of cardiovascular events.

Patients with decreased kidney function had increased prevalence of co-morbidities. In general, they represent a cohort of patients with multiple medical conditions and advanced disease. In particular, diabetes and hypertension were more prevalent in patients with lower eGFR, indicating a possible effect of the type of renal disease (renovascular or diabetes) on outcome. Age appears to modulate the risk conferred by worsening renal function. In the

Table 5 Hazard ratio of death and the composite endpoint associated with different categories of estimated glomerular filtration rate and left ventricular ejection fraction

Endpoint	eGFR category mL/min/1.73 m^2	LVEF <30%		LVEF ≥30%	
		HR	95% CI	HR	95% CI
Death—unadjusted	<30	5.52	4.27–7.14	4.55	3.44–6.00
	30–44.9	3.65	3.16–4.22	2.81	2.40–3.29
	45–59.9	2.18	1.92–2.48	2.03	1.76–2.33
	60–74.9	1.28	1.12–1.47	1.49	1.30–1.72
	75–124.9	1	—	1	—
	125–139.9	0.81	0.47–1.41	0.53	0.25–1.12
Death—adjusted[a]	<30	2.89	2.20–3.81	2.68	2.01–3.57
	30–44.9	2.1	1.80–2.46	1.56	1.32–1.85
	45–59.9	1.54	1.35–1.76	1.41	1.22–1.63
	60–74.9	1.1	0.97–1.27	1.20	1.04–1.39
	75–124.9	1	—	1	—
	125–139.9	0.84	0.48–1.45	0.59	0.28–1.24
Composite—unadjusted	<30	3.66	2.92–4.58	3.51	2.75–4.48
	30–44.9	2.94	2.63–3.28	2.51	2.20–2.85
	45–59.9	1.87	1.70–2.05	1.82	1.63–2.03
	60–74.9	1.25	1.13–1.37	1.4	1.25–1.57
	75–124.9	1	—	1	—
	125–139.9	0.94	0.65–1.36	0.64	0.38–1.07
Composite—adjusted[a]	<30	1.90	1.50–2.41	2.02	1.57–2.60
	30–44.9	1.76	1.56–1.98	1.46	1.27–1.67
	45–59.9	1.38	1.25–1.53	1.30	1.15–1.45
	60–74.9	1.09	0.99–1.20	1.17	1.05–1.31
	75–124.9	1	—	1	—
	125–139.9	0.89	0.61–1.30	0.69	0.41–1.15

Models include eGFR category, LV function, and their interaction (this excludes OPTIMAAL patients from the analysis).
Patients with an eGFR of 75–124.9 mL/min/1.73 m^2 constitute the referent group.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]Adjusted for: age, gender, race, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, smoking history, Killip class, history of diabetes, hypertension, angina, previous myocardial infarction, AF, dyslipidaemia, heart failure, COPD, cerebrovascular disease, and peripheral vascular disease.

current study, older patients did have a worse renal function than younger patients and this was associated with poor outcome. A recent analysis of the American College of Cardiology National Cardiovascular Data Registry showed that, in patients with acute myocardial infarction undergoing primary PCI, the risk of in-hospital mortality imparted by advanced renal insufficiency was greater in those younger than 65 years of age.[26] As an explanation for this observation, severe reduction in eGFR in a younger patient can be regarded as a manifestation of aggressive and advanced underlying disease, as opposed to a similar reduction in an elderly patient. We did not observe a similar finding in our study.

Patients with reduced EF following myocardial infarction are known to have worse prognosis than those with normal EF.[27,28] A single-centre prospective, observational study of patients undergoing primary PCI for acute myocardial infarction stratified patients according to EF (>40% vs. ≤40%) and creatinine clearance by Cockcroft–Gault formula (>60 mL/min vs. ≤60 mL/min). Despite small numbers and short duration of follow-up, patients with both impaired LV systolic and kidney function had worse outcome than those who had either one organ dysfunction or neither.[29] In the setting of acute myocardial infarction and LV dysfunction, impaired renal function can also be a manifestation of reduced kidney perfusion as well as renal congestion, rather than secondary to intrinsic kidney disease alone. Most patients enrolled in our study had LV dysfunction by design (EF ≤40%). We found that lower EF increases the risk associated with renal dysfunction. This finding was strongest in the subgroup of patient with moderately severe kidney dysfunction (eGFR 30–44.9 mL/min/1.73 m^2). In contrast to patients with better or worse kidney function, the risk in this particular group of patients appears to be modulated by cardiac function: those patients with severe cardiac impairment are at an even higher risk than those with less impaired LV systolic function. In patients with more advanced kidney dysfunction, and in those with normal or mildly impaired kidney function, LV function does not seem to alter the risk of events significantly.

In the overall population, a combination of older age and lower LVEF conferred a higher risk of mortality and adverse cardiovascular events across eGFR categories compared with the risk of those who were either younger and/or had better LV function.

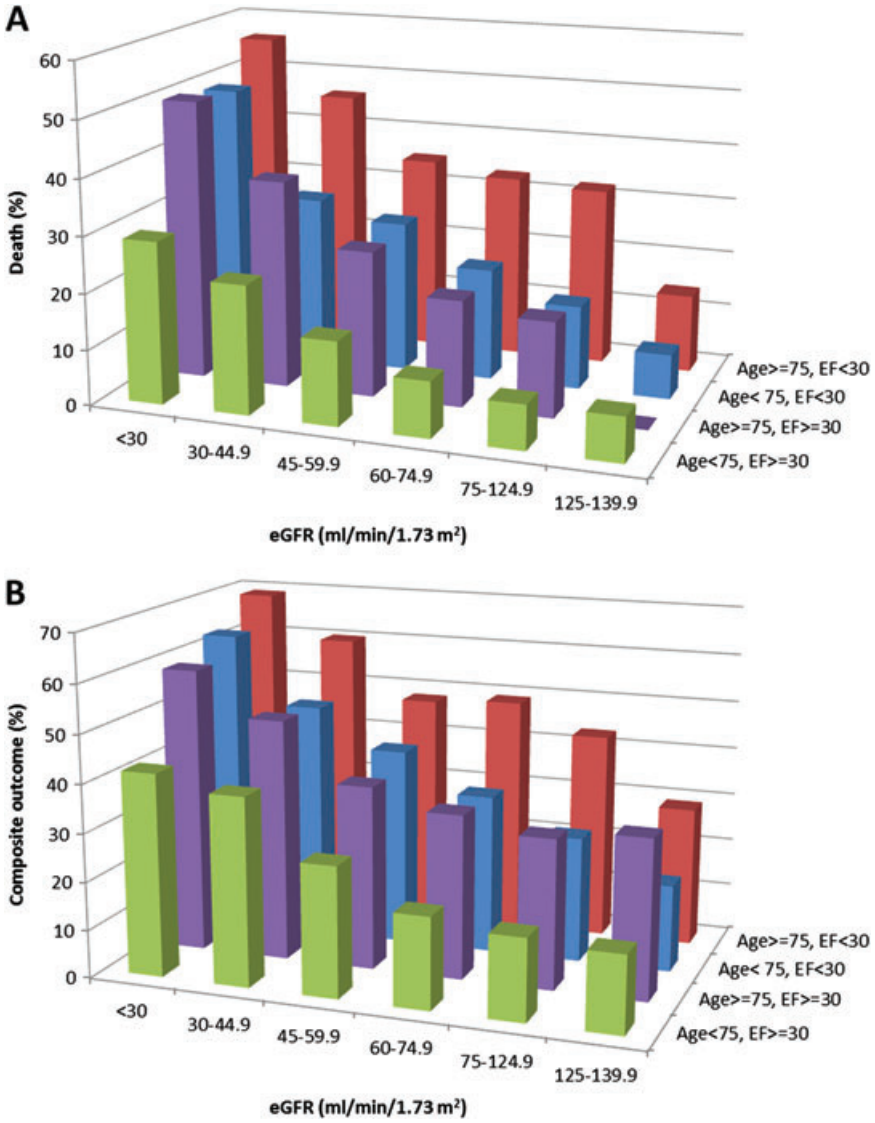

Figure 3 Death (*A*) and composite outcome (*B*) across estimated glomerular filtration rate (eGFR) categories based on age and LV function.

Strengths and limitations

This study is a stratified analysis of four large clinical trials of patients with high risk myocardial infarction, thereby providing the ability to analyse prospectively collected data on a large homogeneous cohort of patients. The independent adjudication of events and the vast amount of data collected during the course of these trials ensure the robustness of the findings. The large sample size provides high statistical power, allowing for precise adjusted analyses. Although the management of myocardial infarction has changed in the past decade, with primary percutaneous revascularization being adopted at many centres for acute myocardial infarction with ST-segment elevation, a vast majority of the patients included in those trials underwent revascularization when appropriate (primary PCI or thrombolysis). The trials included patients with and without ST-segment elevation. Nevertheless, our study has some limitations. The proportion of patients in the lower eGFR categories was small because, by design, most of these trials excluded patients with significant renal dysfunction (creatinine >2.5 mg/dL). Therefore, the results are less robust in this patient subgroup. We used the MDRD equation to estimate GFR, while recognizing that this method has its inherent limitations, but performs better in patients with lower GFR than other equations (eg. Chronic Kidney Disease Epidemiology Collaboration—CKD-EPI).[30] We did not account for change in renal function over time, which can potentially add predictive information to the baseline one-time measurement. We did not have information on the presence of proteinuria and were not able to explore its relationship to outcomes. We did not test for interaction with study drug because the merged data set does not include study drug assignment of each trial. Finally, our study population consisted mainly of Caucasians,

with the majority being males, which limits the generalizability of the findings to a different population.

Conclusions

In patients following myocardial infarction complicated by clinical signs of heart failure and/or evidence of LV dysfunction, renal dysfunction as evidenced by low eGFR is associated with worse outcome and increased incidence of adverse cardiovascular events. This graded relationship is true across the spectrum of kidney function studied in these four trials. Worse kidney function is associated with multiple co-morbidities; clinical characteristics, such as LV systolic function and age, may modulate the increased risk these patients.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of eGFR values among the 27 610 patients across the 4 trials.

Figure S2. Kaplan-Meier estimates of the event rates at 3 years for death, cardiovascular death, heart failure hospitalization, myocardial infarction, stroke, and the composite endpoint, by eGFR category.

Table S1. Outcomes across eGFR categories based on age and left ventricular function.

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Conflict of interest: Z.-F.Y. and Y.H. have received fees for participation in statistical analysis from Statistics Collaborative, Inc. J.T.W. is an employee of Statistics Collaborative which has had contracts with Merck, Roche, Novartis, and Pfizer. None of the contracts was relevant to the topic of the manuscript. B.P. has received compensation for board membership of Aurasence; consultancy fees from Pfizer, Gambro, Bayer, Takeda, Mesoblast, Amorcyte, Lilly, Relypsa, BG-medicine, and Merck; grants from Forrest Laboratories; meeting expenses from Pfizer, Bayer, Gambro, and Mesoblast; and has stocks in Relypsa, Aurasence, BG-medicine, and scTherapeutics. F.Z. has received a grant from Roche—Biomérieux; consulting fees from Pfizer, Novartis, ResMed, Bayer, Servier, Takeda, Johnson & Johnson, and Boston Scientific; compensation for board membership of Boston Scientific; consultancy fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and ResMed; grants from BG Medicine and Roche Diagnostics; and payment for lectures from Pfizer and AstraZeneca. M.A.P. has received consulting fees from Aastrom, Amgen, Anthera, Bayer, Boehringer, Bristol-Myers Squibb, Cerenis, Concert, Genzyme, Karo Bio, Keryx, Merck, Roche, Servier, Teva, and Xoma; grants from Amgen, Celladon, Sanofi Aventis, and Novartis; and is a co-inventor of patents with Novartis and Boehringer. S.D.S. has received a grant from Novartis, and consultancy fees from Novartis. All other authors have no conflicts to declare.

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